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Graft-versus-Host Disease of the Vulva and/or Vagina: Diagnosis and Treatment

Lisa B. Spiryda,[1] Marc R. Laufer,[1] Robert J. Soiffer,[2] Joseph A. Antin[2]

[1]Department of Obstetrics, Gynecology, and Reproductive Biology, and [2]Department of Medicine, Brigham and Women's Hospital and Dana Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts

Correspondence and reprint requests: Marc R. Laufer, MD, Division of Gynecology, Children's Hospital, 300 Longwood Ave., Boston, MA 02115 (e-mail: marc.laufer@tch.harvard.edu).

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ABSTRACT

We describe a series of women after allogeneic stem cell transplantation with vaginal graft-versus-host disease (GVHD) who were treated with topical cyclosporine, surgery, or both. We reviewed the medical charts of 11 women who presented with vaginal pain, discomfort, and vaginal scarring (inability to perform a Papanicolaou test or have vaginal intercourse because of pain). Vaginal symptoms develop an average of 10 months from bone marrow transplantation. Symptoms and physical findings include excoriated and ulcerated mucosa, thickened mucosa, narrowed introitus, and obliterated introitus from dense scar tissue that does not resolve with systemic or topical estrogens. The severity of symptoms and the physical findings in our study population did not correlate with age, type of leukemia, type of transplant, or severity or acute or chronic GVHD. Excoriated mucosa and moderately thickened mucosa were successfully treated with topical cyclosporine. Extensive synechiae and complete obliteration of the vaginal canal required surgical lysis with postoperative topical cyclosporine. Vaginal GVHD can successfully be treated with topical cyclosporine when mild to moderate disease is present. Surgical lysis with topical cyclosporine is required when more severe disease ensues.

KEY WORDS

Vagina • Graft-versus-host disease

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is frequently performed to treat disorders of the blood and immune system. It is often complicated by graft-versus-host disease (GVHD). The pathogenesis of both acute and chronic GVHD is believed to be a complex immune response, primarily T-cell mediated, in which the grafted donor cells recognize the host as foreign. The effects of this condition are well described involving the skin, gastrointestinal tract, lung, and liver [1-3].

After an HSCT, women frequently present with vulvar or vaginal complaints of dryness, irritation, dyspareunia, and postcoital bleeding. These symptoms are generally attributed to lack of adequate estrogenization of the vulvar and vaginal mucosa, because most women experience premature ovarian failure secondary to the transplant conditioning regimen. There is increasing evidence in the literature that this vulvar/vaginal symptomatology may be due, at least in part, to GVHD [5-10]. We present a series of women after HSCT with these symptoms who did not respond to topical and systemic estrogen therapy and who were believed to have GVHD of the vulva and vagina. These women were treated with topical immunosuppressive therapy and vaginal dilators, and some required surgery. This is the first series of patients in whom topical immunosuppressive agents were used in the treatment of genital GVHD.

MATERIALS AND METHODS

Medical charts of 11 women's status after bone marrow transplantation with vaginal symptoms that were not responding to estrogen therapy (Table 1) were reviewed. Approval was obtained from the institutional review board of Brigham and Women's Hospital. Conditioning regimens used in the study popu-

Table 1. *Severity of GVHD*

Subject No.	Leukemia	Age at HSCT	Type of HSCT	Severity of Acute GVHD	Severity of Chronic GVHD	Severity of Vulva/Vaginal Physical Findings
1	Myelodysplastic syndrome	34	Matched related	Mild	Mild to moderate	Moderate
2	AML	25	Matched unrelated	None	None	Severe
3	CLL	44	Matched unrelated	Mild	Severe	Severe
4	CML	47	Matched unrelated	Moderate	Mild	Moderate
5	CML	54	Matched related	Moderate	Severe	Moderate
6	Myelodysplastic syndrome/AML	37	Matched related	Mild	Mild	Severe
7	AML	51	Matched related	Mild	None	Severe
8	ALL/AML	25/27	Matched unrelated	1 mild, 2 none	Mild to moderate	Moderate
9	Lymphocytic leukemia	28	Matched related	Moderate	Mild	Mild
10	AML	23/26	Matched unrelated	1 none, 2 none	1 mild, 2 moderate	Moderate
11	CLL	59	Matched unrelated	Mild	Moderate	Severe

AML indicates acute myeloid leukemic; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; ALL, acute lymphocytic leukemia.

lation included cyclophosphamide plus total body irradiation (14 Gy) or busulfan/cyclophosphamide. All transplant recipients received bone marrow as the source of stem cells. GVHD prophylaxis was systemic cyclosporine and methotrexate or tacrolimus and methotrexate administered according to standard schedules. Chronic GVHD was also treated with systemic cyclosporine and steroids with standard tapers once symptoms had abated.

All women were initiated on hormone-replacement regimens at the time of transplantation for treatment prophylaxis for ovarian failure. Women who had persistent vaginal pain, discomfort, vaginal scarring (inability to perform a Papanicolaou test or have vaginal intercourse because of pain), or postcoital bleeding were referred to one of the authors of this study. All referred patients were included in our study population and had physical findings not consistent with a hypoestrogenic vulva or vagina.

Cyclosporine vaginal cream was compounded by using 200 mg of the oral suspension of cyclosporine with evaporation of the alcohol and placed in a vehicle of 5 g of an anhydrous ointment base. Cyclosporine vaginal cream was compounded because at the time of initial evaluation of these patients, topical tacrolimus was not commercially available. The standard regimen for cyclosporine cream in our patient population was application 2 times a day for 4 weeks, followed by a taper over the next 2 months. Flares of vulvar and vaginal symptoms were treated in a similar manner.

RESULTS

Tables 1 to 3 summarize the data from our series. The women ranged in age from 25 to 59 years at the time of leukemia diagnosis and HSCT. All patients in this series received high-dose cyclophosphamide and total body irradiation as a conditioning regimen before transplantation. Five women underwent a sibling-matched transplantation, and 6 received a matched unrelated donor transplant. After the transplantation,

Table 2. *Treatment Regimens for Vaginal and Vulva GVHD*

Subject No.	Time from HSCT to Development of Vaginal Symptoms	Systemic Estrogens	Topical Estrogens	Preoperative Topical Cyclosporine	Surgery
1	5 mo	Yes	Yes	Yes	Yes
2	3 mo	Yes	No	No	Yes
3	6 mo	Yes	Yes	Yes	Yes
4	14 mo	Yes	Yes	Yes	No
5	5 mo	Yes	Yes	Yes	No
6	13 mo	Yes	No	Yes	Yes
7	24 mo	Yes	No	No	Yes
8	8 mo from No. 2	Yes	No	Yes	Yes
9	9 mo	Yes	No	Yes*	No
10	18 mo from No. 2	Yes	Yes	Yes	No
11	8 mo	Yes	Yes	Yes	Yes

*Tacrolimus.

Table 3. *Pathology and Current Status*

Subject No.	Pathology	Postoperative Cyclosporine	Current Status
1	N/A	Yes	HSIL/VIN, minimal scarring
2	Stromal tissue with chronic inflammation	Yes	Minimal scarring
3	Lichenoid dermatitis	Yes	Dead
4	Spongiotic dermatitis	N/A	HSIL, minimal scarring
5	N/A	N/A	Dead
6	N/A	Yes	Resolved with systemic cyclosporine
7	Hyperkeratotic and inflamed epithelium and stroma	Yes	Minimal scarring
8	Epithelium with inflammation and parakeratosis	Yes	Minimal scarring
9	N/A	N/A	Minimal scarring
10	Subacute spongiotic dermatitis	N/A	Dead
11	Stromal tissue with inflammation	Yes	Minimal scarring

N/A indicates not available; HSIL, high-grade squamous intraepithelial lesion; VIN, vulvar intraepithelial neoplasm.

all women were maintained on a short course of systemic cyclosporine GVHD prophylaxis. Additionally, these women were placed on either estrogen 0.625 mg/progesterone 2.5 mg or estrogen 0.625 mg/methyltestosterone 1.25 mg with progesterone 2.5 mg each day as hormone replacement therapy for ovarian failure. Nine women developed mild to moderate acute GVHD that was treated with a short course of systemic prednisone (Table 1). Seven women developed mild to moderate GVHD treated with systemic cyclosporine and prednisone during flares according to standard dosing regimens. Two women had severe GVHD; these women ultimately died from complications from the GVHD (Tables 1 and 3).

These patients developed vaginal symptoms on average 10.2 months (range, 3-24 months) after HSCT (Table 2). The most common presenting vaginal complaints were dryness, itching, and pain to touch. These symptoms ultimately led to dyspareunia and the inability to have vaginal intercourse. Although the symptoms experienced by these women often closely mimicked those associated with ovarian failure, the physical features found on pelvic examination were striking and did not resemble those found during menopause (either induced or natural).

On physical examination, most patients with moderate vaginal GVHD had narrowing of the vagina, with thickening of the mucosa and adhesive bands. The synechiae most commonly either obliterated the upper vaginal canal or developed circumferentially around the introitus. At times as the GVHD progressed, the adhesions foreshortened the vaginal canal, leading to the inability to visualize the cervix or perform a Papanicolaou test. Other common findings on the vulva and vagina in milder cases were open, flat sores and erythematous and excoriated mucosa that was tender and friable to touch. It should be noted that all cultures of open lesions were negative for herpes simplex virus. In our series, these mild features progressed to the more moderate synechiae if patients did not use the cyclosporine cream on a regular basis.

Although the number of patients was small, after we reviewed the medical charts, it was clear that the onset of vulvar or vaginal GVHD did not occur or worsen with flares in other organ systems, including skin and oral mucosa. Systemic cyclosporine and steroids did not abate gynecologic findings except in 1 patient (patient 6). In our series, the severity of vaginal GVHD also did not correlate with age at the time of transplantation or the type of HSCT (Table 1). This is interesting because factors that predict the severity of chronic GVHD are older age at the time of HSCT, matched unrelated transplant, and aggressive acute GVHD [1].

Treatment regimens for the vaginal symptoms initially included topical estrogens in 6 of the 11 patients. Topical estrogens were not successful in abating the symptoms and physical findings in any of these 6 patients (Table 2). Topical cyclosporine was initiated in 9 patients before surgical intervention, and 5 of these patients ultimately required surgery. Two patients were immediately taken to surgery because of severe vaginal stenosis (Table 2). Topical cyclosporine was most successful in treating women with ulcerated and excoriated tissue on the vulva and vagina. Skin integrity improved after 2 weeks of cyclosporine. This topical regimen was also successful in the treatment of moderate thickening of the vaginal mucosa; its effects were ameliorated when it was used in concert with vaginal dilators. Improvements in clinical manifestations of GVHD were sufficient to avoid surgical interventions in 4 patients.

Surgery was necessary for 7 of the 11 women (Table 2). After surgery, all patients used topical cyclosporine with vaginal dilators (Table 3). By 6 to 12 weeks after surgery, these patients were able to resume vaginal intercourse. In one patient (patient 6), neither topical cyclosporine nor surgery was able to ameliorate her physical findings or symptoms. Her vaginal synechiae were thick and dense. Her symptoms ultimately abated with systemic cyclosporine and pred-

nisone (Table 3). It should be noted that she had minimal to no GVHD at other sites.

Two of the patients (patients 2 and 7) had almost complete obstruction of the entire vaginal canal at the time of presentation, so a trial of topical cyclosporine was not initiated. These patients were directly taken to the operating room for surgical lysis of adhesions and re-creation of the caliber and length of the introitus. After surgery, these women used topical cyclosporine and vaginal dilators and resumed sexual activity after 2 months.

Five patients (patients 1, 3, 6, 8, and 11) were initially started on topical cyclosporine but ultimately required surgery (Table 2). Patients 3, 6, and 8 did not complain of any vaginal symptoms until findings were severe. In these cases, the synechiae were already dense and obliterated most of the vaginal canal. Topical cyclosporine was used as a temporizing agent in these cases to soften the adhesions before surgery. Of note, patient 3 had been treated with topical estrogens for longer than 1 year before referral to gynecology. During this time, her vaginal disease substantially progressed. Patients 1 and 11 both initially presented with mild disease and were successfully treated with topical cyclosporine. Both patients stopped using the cream when symptoms resolved. These patients did not require additional therapy until vaginal intercourse was not possible. Adhesive bands had formed rapidly over the ensuing months when no topical cyclosporine was used. At this point, the topical regimen only softened the synechiae, and the patients required surgical lysis. It should be noted that the topical cyclosporine had to be compounded by a pharmacist and was very expensive; it was not always covered by insurance plans. This may have contributed to lack of patient compliance for long-term use of this medication in these women.

The pathology of affected vaginal and/or vulvar mucosa was obtained in 7 women in our series (Table 3). The most common histologic finding was foci of chronic and acute inflammation within the stroma and epithelium. Additionally, lichenoid dermatitis (patient 3), spongiotic dermatitis (patients 4 and 10), and hyperkeratosis (patients 7 and 8) were observed. These pathologic findings were consistent with mucosal and skin findings in classic chronic GVHD [11].

Two of the women in our series developed persistent high-grade squamous intraepithelial lesions, which were detected by Papanicolaou test and confirmed by biopsy and colposcopy (Table 3; patients 1 and 4). Patient 1 underwent large loop excision of the transformation zone, and all subsequent Papanicolaou tests have been normal. Patient 4 had persistent high-grade squamous intraepithelial lesions despite colposcopy-guided laser treatment, and she underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy. Final pathology revealed no invasive cervical disease but did show dysplasia of the vaginal vault. The dysplasia of the vaginal cuff persisted on biopsy, and the patient underwent another laser procedure. Since that time, all Papanicolaou tests have been within normal limits. All other women in our series have had normal Papanicolaou tests since the time of HSCT and topical cyclosporine use.

DISCUSSION

GVHD is a major complication after allogeneic HSCT; however, involvement of the vagina has not been well characterized. Vaginal GVHD was first described in 1982 by Corson et al. [5] in 5 women with sclerosing vaginitis and stricture formation. Since then, several cases have been reported with complete vaginal blockage leading to the formation of hematocolpos [6-10]. Vaginal stenosis limits the ability to perform a routine Papanicolaou test and prevents vaginal intercourse. Vulvar excoriations can be painful. Various treatment regimens have been advocated, including topical estrogens, surgical lysis, and vaginal dilators, with marginal benefit.

This series describes 11 women who developed GVHD of the vagina and vulva after allogeneic stem cell transplantation despite receiving systemic cyclosporine and steroids immediately after transplantation. From our series and other reports of vaginal stenosis and agglutination, it seems that this form of chronic GVHD develops on average 10.2 months after transplantation [5-10], but symptoms can also develop as late as 2 years after the transplantation. In several of our patients, biopsy samples were obtained of the affected region. Histologic features were varied (Table 3), but all revealed patterns similar to those found on skin affected with chronic GVHD [12]. In this small series, vaginal GVHD did not occur more frequently in women who received an HSCT from a matched unrelated donor than from a sibling-matched donor (Table 1). It should be noted that the severity of vaginal and vulvar symptoms did not correlate with the severity of acute or chronic GVHD found in other organ systems. Some women with severe vaginal stenosis have only mild chronic GVHD. This is similar to case reports reported in the literature [5-10].

In our series, all of the women initially received systemic estrogen therapy at the time of HSCT, and 6 of the patients used topical estrogen for vaginal and vulvar atrophy. It has been reported that hormone-replacement therapy does not influence the severity or activity of GVHD and can be safely used as a prophylactic measure to treat ovarian failure [13]. The changes on the vulvar and vaginal mucosa could not solely be attributed to their hypoestrogenic state. Hypoestrogenized vaginal and vulvar mucosa is characterized by thin and atrophic mucosa that responds to

topical estrogen. The women from our series clearly had different physical findings. Synechiae and adhesive bands are never found on examination of menopausal women. Although the vagina may lose some elasticity, it will not become obliterated with scar tissue that obscures the cervix. The findings in our women, as well as those in case reports [6-10], indicate that GVHD is a distinct entity from the hypoestrogenic state of the tissue experienced with ovarian failure.

In prior studies, women were not treated until the vagina was completely obliterated, which required surgical intervention [6-9]. We found that topical cyclosporine was successful in treatment of vaginal and vulvar GVHD. This treatment was very successful in treating the skin changes found on the vulva after several weeks of application. The response to vaginal synechiae was varied. When minimal to moderate scarring was found, cyclosporine cream was successful in preventing surgery (Table 2). Sometimes these women required vaginal dilators to help relieve the symptoms. When women presented with extensive scarring, partial obstruction of the vagina, and inability to visualize the cervix, the cyclosporine cream did help to soften the scar tissue, but the women required surgical lysis of the adhesions. After surgery, all women continued with cyclosporine cream and dilators until they were able to resume vaginal intercourse. The cyclosporine cream seemed to prevent any new scarring from developing, and patients continued to use it as needed. No patient required a second operation (Table 3).

Several questions arise from this small case series. First, we do not know the true incidence of vaginal GVHD. This series was collected in a busy transplantation program over 10 years. During this interval, 501 transplantations were performed in women. It is possible that many women with vulvovaginal GVHD did not have symptoms, did not discuss them with the transplant team, or, possibly, believed that these symptoms were not a GVHD complication. It is likely that a number of women are not sexually active after HSCT, and this may further increase the ascertainment bias.

Second, all the women except 1 in our series had been receiving systemic cyclosporine while they developed these symptoms, but there seemed to be substantial benefit from the additional topical therapy. Topical cyclosporine has not been effective in skin or oral mucosal GVHD. This raises the possibility that the efficacy of topical therapy in the genital region is due to a presumed prolonged exposure time to the affected mucosa. The topical cyclosporine was specifically formulated and not commercially available. One patient (patient 9) did successfully use tacrolimus. It would be interesting to determine in a larger study whether tacrolimus is similarly effective. It is possible that topical cyclosporine may successfully prevent vaginal adhesions and vulvar skin changes, obviating the necessity for surgical intervention when applied early, thus indicating the importance of taking a sexual history in the posttransplantation period. The women with the most resistant vaginal GVHD that required surgery had fairly extensive adhesions at the time of diagnosis.

Another important question that arises from this data is as follows: does topical application of immunosuppressive agents such as cyclosporine lead to increased frequency of dysplasia of either the cervix or vagina? Two women in our series did require treatment for persistent dysplasia. Cyclosporine may make the vaginal mucosal cells or cervical cells more susceptible to infection with human papillomavirus, which may lead to dysplasia. Clearly, a larger series of women will need to be examined. Of note, in one retrospective analysis of cervical cytology, women after allogeneic bone marrow transplantation had higher rates of cytologic abnormalities (presumably related to conditioning), and these women may require more frequent screening [12].

Vulvar and vaginal GVHD seems to be a discrete entity in the continuum of chronic GVHD. As more studies are performed, women who experience these complications can promptly and effectively be treated.

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